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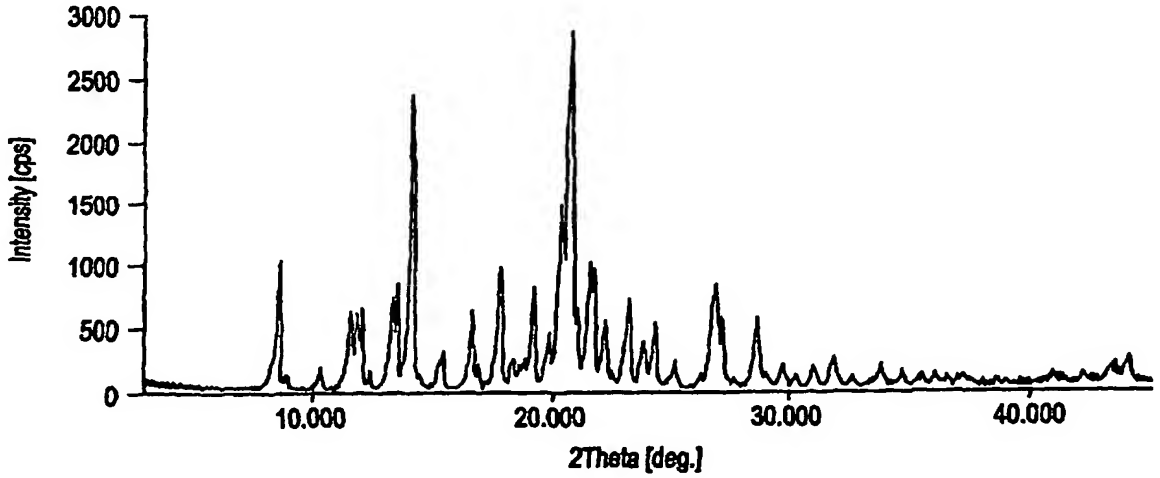
(54) Title: NOVEL CRYSTALLINE POLYMORPH FORM-VI OF OLANZAPINE AND A PROCESS FOR PREPARATION THEREOF



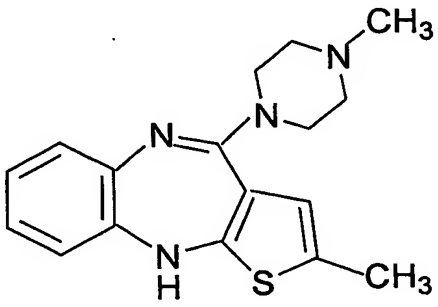
(57) Abstract: The present invention relates to a novel crystalline form of 2-methyl-4-(4-methyl-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and to a method of preparation thereof. Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine (Olanzapine) is represented by Structure (I).

WO 2003/091260 A1

NOVEL CRYSTALLINE POLYMORPH FORM-VI OF OLANZAPINE AND A PROCESS FOR PREPARATION THEREOF

FIELD OF INVENTION

The present invention relates to a novel crystalline form of 2-methyl-4-(4-methyl-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and to a method of preparation thereof. Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine (Olanzapine) is represented by the following Structure.



The present invention also relates to compositions made using the crystalline form of 2-methyl-4-(4- methyl-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and the use of crystalline form and compositions made using the crystalline form for the treatment of disorders of the central nervous system, for treating psychotic patients and mild anxiety.

BACKGROUND OF INVENTION

U.S. 5,229,382 discloses the preparation of Olanzapine and its acid addition salts, having pharmaceutical properties, particularly in the treatment of disorders of the central nervous system. The patent does not refer to any specific polymorphic crystalline forms of Olanzapine.

EP 0 733 635 A1 claims Form-2 of Olanzapine. The patent also states that the product obtained according to the process described in U.S. 5,229,382 as Olanzapine Form-I.

Furthermore, EP 0 733 635 A1 discloses the d values for Form-1 and Form-2 from their X-ray Diffractograms. The d values are as follows:

d value	**d value**
Form-1	**Form-2**
9.94	10.26

8.55	8.57
8.24	7.47
6.88	7.12
6.37	6.14
6.24	6.07
5.58	5.48
5.30	5.21
4.98	5.12
4.83	4.98
4.72	4.76
4.62	4.71
4.53	4.47
4.46	4.33
4.29	4.22
4.23	4.14
4.08	3.98
3.82	3.72
3.74	3.56
3.69	3.53
3.58	3.38
3.50	3.25
3.33	3.12
3.28	3.08
3.21	3.06
3.11	3.01
3.05	2.87
2.94	2.81
2.81	2.72
2.75	2.64
2.65	2.60
2.63	
2.59	

EP 831098B1 discloses Olanzapine Form-II as the most stable anhydrous form of Olanzapine, providing a stable anhydrous formulation with pharmaceutically desired characteristics. The patent further discloses that substantially pure Olanzapine Form-II, which can be prepared using an Olanzapine dehydrate. In addition to this, the patent discloses the preparation of a series of dihydrates of Olanzapine namely Dehydrate B, Dehydrate D and Dehydrate E characterized by their XRD pattern which serve as intermediates for the preparation of Olanzapine Form-II.

U.S. 6,348,458 B1 discloses the preparation of a series of crystalline polymorphic forms of Olanzapine namely Form-III, Form-IV and Form-V. The d values for these forms from their X-Ray Diffractograms are also incorporated in the patent and are mentioned in the following Table-1.

Form-III	Form-IV	Form-V
d value	d value	d value
10.7476	9.9487	10.5932
10.3156	8.5074	10.217
8.6245	8.2103	9.9503
7.1713	6.8673	8.5259
6.5014	4.9734	7.1016
6.112	4.8172	6.0731
5.9251	4.7114	5.2041
5.8243	4.6122	4.9856
5.5165	4.5282	4.8153
5.2359	4.234	4.7514
4.8541	4.0901	4.6139
4.7514	3.7574	4.5302
4.5578	3.6989	4.4714
4.4938	3.5052	4.2271
4.4536		4.1307
4.2588		4.0736
4.1523		3.988
4.0699		3.7763
3.9898		3.7167
3.8955		3.5315
3.7288		3.3762
3.5626		3.006
3.0262		

WO 02/18390 discloses Olanzapine monohydrate I and Olanzapine dehydrate I and process for making these compounds.

The novel crystalline polymorphic form of Olanzapine of the present invention is well distinguished from the crystalline polymorphic forms reported in the prior art and conveniently herein after, designated as Polymorph Form-VI of Olanzapine. Hence present invention provides a novel crystalline polymorph Form-VI of Olanzapine and the present invention also embodies the process for the preparation of crystalline polymorph Form-VI of Olanzapine, more specifically the present invention is related to conversion of Polymorph Form-I of Olanzapine to novel crystalline polymorph Form-VI of Olanzapine.

SUMMARY OF THE INVENTION

The present invention provides a novel crystalline polymorphic Form of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b] [1,5] benzodiazepine (Olanzapine), conveniently designated as Polymorph Form-VI of Olanzapine. The invention also relates to provide the process for the preparation of crystalline polymorph Form-VI of Olanzapine, which comprises stirring of polymorph Form-I of Olanzapine in a C_1-C_6 alkanol to obtain the novel crystalline polymorph Form-VI of Olanzapine.

The process of the present invention is eco friendly and well suited for industrial scale up.

BRIEF DESCRIPTION OF ACCOMPANYING DRAWINGS

Fig. 1 is an X-ray powder diffractogram of the Form VI obtained in the present invention.

Fig. 2 is a DSC thermogram of the Form VI obtained in the present invention.

Fig. 3 is an infrared absorption spectrum of the Form VI obtained in the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention provides novel crystalline polymorph Form-VI of Olanzapine and a process for the preparation thereof.

The Crystalline nature of polymorph Form-VI of Olanzapine can be characterized by its X-ray diffractogram, Infrared spectrum and Differential scanning calorimetry thermogram.

The X-ray powder diffraction pattern of crystalline polymorph Form-VI of Olanzapine was measured on a Rigaku D/Max 2200 Powder Diffractometer with Cu

Radiation source. The Crystalline polymorph Form-VI of Olanzapine has X-ray powder diffraction pattern essentially as shown in the Table-2. The X-ray powder diffraction pattern is expressed in the terms of its d values, and percentage intensity (in %).

TABLE 2

d-values	Intensity (%)
10.2972	35
8.5646	6
7.6618	22
7.4935	21
7.3691	21
6.6317	25
6.5246	29
6.2320	87
5.7713	7
5.7121	9
5.3042	20
5.2174	6
4.9733	34
4.8335	7
4.7614	5
4.7162	8
4.6284	27
4.4802	13
4.3795	54
4.3163	77
4.2874	100
4.2308	21
4.1297	34
4.0958	34
4.0117	17
3.8275	24
3.7263	13
3.6509	17
3.5311	6
3.3141	29
3.2782	18
3.1207	17
3.0035	5
2.8824	5
2.8099	8
2.8014	6

d-values	Intensity (%)
2.0562	6

The present invention of crystalline polymorph Form-VI of Olanzapine is characterized by its X-ray powder diffraction as depicted in Figure (1).

The present invention also provides Differential Scanning Calorimetry thermogram of crystalline polymorph Form-VI of Olanzapine. The Differential Scanning Calorimetry thermogram exhibits a significant endo peak around 196°C and as depicted in Figure (2).

The present invention further provides the Infrared data for crystalline polymorph Form-VI of Olanzapine, which was measured by KBr-transmission method with identified significant peaks around 3217 cm^{-1}, 2933 cm^{-1}, 1592 cm^{-1}, 1561 cm^{-1}, 1468 cm^{-1}, 1369 cm^{-1}, 1218 cm^{-1}, 1143 cm^{-1}, 1007 cm^{-1}, 964 cm^{-1}, 751 cm^{-1} and 674 cm^{-1}. The present invention provides the IR spectrum of crystalline polymorph Form-VI of Olanzapine as depicted in Figure (3).

Accordingly, the present invention provides novel crystalline polymorphic Form-VI of 2-methyl-4- (4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine (Olanzapine), which comprises:

i) stirring polymorph Form-I of Olanzapine in a C_1-C_6 alkanol at a temperature of 0 to 40°C for 30 minutes to 10 hours;

ii) isolating the obtained solid form step (i) by conventional methods;

iii) drying the compound of step (ii) at a temperature of 40 to 100°C to afford the desired crystalline polymorph Form-VI of Olanzapine.

Preferably, the alkanol is n-butanol or tert.butanol. More preferably the alkanol is n-butanol.

Preferably, the solid obtained in step 2) is isolated by filtering, decanting or centrifuging.

The present invention therefore provides novel Olanzapine Form-VI and a simple method for its preparation.

The polymorph Form-I of Olanzapine was prepared as per the procedure disclosed in WO 02/18390 A1 the disclosure of which is incorporated by reference. A mixture of 4-amino-2-methyl-10H-thieno-[2,3-b] [1,5]benzodiazepine HCl (100 g), N-methyl piperizine (350ml), DMSO (465 ml) and toluene (465 ml) was heated to

reflux. The reaction mass was maintained at reflux for 19 hours and then cooled to 50°C and water was added. The reaction mass was cooled to 0-10°C and stirred at the same temperature for 6 hours. The crude Olanzapine separated was filtered and dried in oven to a constant weight (76.5 g). The crude compound was added to acetonitrile (750 ml) at boiling temperature. The mixture was boiled for further 5 minutes. The mixture was filtered to remove the undissolved solid. The filtrate was treated with carbon and filtered. The filtrate was distilled to a minimum volume, cooled to 0-5°C and maintained at the same temperature for 1.0 hour and filtered. The compound was dried to a constant weight in an oven (51.6g).

Form I can be prepared by any other method.

The invention likewise relates to the use of novel crystalline of 2-methyl-4-(4- methyl-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine useful in the treatment of disorders of the central nervous system, for treating psychotic patients or mild anxiety. It can be used to prepare pharmaceutically acceptable preparations, in a method for the prophylactic and/or therapeutic treatment of an animal or human.

The invention likewise relates to pharmaceutical preparations made using the novel crystalline of 2-methyl-4-(4- methyl-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and to processes for their preparation.

The pharmaceutical preparations according to the invention which contain the compound according to the invention are those for enteral, such as oral, furthermore rectal, and parenteral administration to (a) warm-blooded animal(s), the pharmacological active ingredient being present on its own or together with a pharmaceutically acceptable carrier. The daily dose of the active ingredient depends on the age and the individual condition and also on the manner of administration.

The novel pharmaceutical preparations contain, for example, from about 10% to about 80%, preferably from about 20% to about 60%, of the 2-methyl-4-(4-methyl-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine. Preferably, the compositions are formulated in unit dosage form, each dosage containing from 0.1 mg to 20 mg or 0.5 to 10 mg of the 2-methyl-4-(4- methyl-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine. Pharmaceutical compositions of this invention can contain and/or comprise a therapeutically effective amount of the 2-methyl-4-(4- methyl-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine made from the novel crystalline form of this

invention, together with one or more inorganic or organic, solid or liquid, pharmaceutically acceptable carriers, diluents, excipients, additives, fillers, lubricants, binders, stabilizers, solvents or solvates. The compositions may be in the form of a tablet, capsule, lozenge, powder, syrup, solution, suspension, ointment or dragee. The pharmaceutical compositions may be sterilized and/or may comprise of one or more excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating the osmotic pressure and/or buffers. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

Suitable carriers are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, furthermore binders, such as starch paste, using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired, disintegrants, such as the above mentioned starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate; auxiliaries are primarily glidants, flow-regulators and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Sugar-coated tablet cores are provided with suitable coatings which, if desired, are resistant to gastric juice, using, inter alia, concentrated sugar solutions which, if desired, contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of gastric juice-resistant coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colorants or pigments, for example to identify or to indicate different doses of active ingredient, may be added to the tablets or sugar-coated tablet coatings.

Other orally utilizable pharmaceutical preparations are hard gelatin capsules, and also soft closed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The hard gelatin capsules may contain the active ingredient in the form of granules, for example in a mixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and, if desired, stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it also being possible to add stabilizers.

Suitable rectally utilizable pharmaceutical preparations are, for example, suppositories, which consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Furthermore, gelatin rectal capsules which contain a combination of the active ingredient with a base substance may also be used. Suitable base substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable preparations for parenteral administration are primarily aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and furthermore suspensions of the active ingredient, such as appropriate oily injection suspensions, using suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if necessary, also stabilizers.

The dose of the active ingredient depends on the warm-blooded animal species, the age and the individual condition and on the manner of administration. In the normal case, an approximate daily dose of about 10 mg to about 350 mg is to be estimated in the case of oral administration for a patient weighing approximately 75 kg. For other types of administration, the preferred daily dose is between 0.1 mg to 1000 mg per kilogram, preferably between 1 mg to 100 mg daily for warm-blooded species. More, preferably, between 1 mg to 40 mg daily.

DETAILED DESCRIPTION OF ACCOMPANYING DRAWINGS

Fig. 1 is a characteristic X-ray powder diffraction pattern of novel

crystalline-polymorph Form-VI of Olanzapine.

(Vertical axis: Intensity (CPS); Horizontal axis: 20(degrees).

The significant d values obtained are 10.2972, 8.5646, 7.6618, 7.4935, 7.3691 6.6317, 6.5246, 6.2320, 5.7713, 5.7121, 5.3042, 5.2174, 4.9733, 4.8335, 4.7614, 4.7162, 4.6284, 4.4802, 4.3795, 4.3163, 4.2874, 4.2308, 4.1297, 4.0958, 4.0117, 3.8275, 3.7263, 3.6509, 3.5311, 3.3141, 3.2782, 3.1207, 3.0035, 2.8824, 2.8099, 2.8014 and 2.0562 A°.

Fig. 2 is a characteristic Differential Scanning Calorimetric thermogram of novel crystalline polymorph of Form-VI of Olanzapine.

Vertical axis: Temperature (in °C); Horizontal axis: Signal (in mV).

The Differential Scanning Calorimetric Thermogram exhibits a significant endo peak at 196°C.

Fig. 3 is a characteristic infrared absorption spectrum in potassium bromide of Olanzapine Form-VI.

[Vertical axis, Transmission (%); Horizontal axis: Wave number (cm^{-1})].

The characteristic peaks for Olanzapine Form-VI are indicated around 3217 cm^{-1}, 2933 cm^{-1}, 1592 cm^{-1}, 1561 cm^{-1}, 1468 cm^{-1}, 1369 cm^{-1}, 1218 cm^{-1}, 1143 cm^{-1}, 1007 cm^{-1}, 964 cm^{-1}, 751 cm^{-1} and 674 cm^{-1}.

EXAMPLES

The present invention is described in detail with example given below that are provided by way of illustration only and therefore, should not be construed to limit the scope of the invention.

PREPARATION OF CRYSTALLINE POLYMORPH FORM-VI OF OLANZAPINE

EXAMPLE 1

A mixture of polymorph Form- I of Olanzapine (10.0 g) and n-butanol (30 ml) was stirred at a temperature of 25 - 30°C for 1-2 hours. Further the compound was filtered, washed with n-butanol (5.0 ml) and dried at a temperature of 60 - 70°C to a constant weight to render the desired crystalline polymorph Form-VI of Olanzapine.

(Yield: 7.1 grams, 71.0%).

CLAIM

1. A novel crystalline polymorph Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine (Olanzapine).

2. The crystalline polymorph Form-VI of Olanzapine of claim 1 having X-ray powder diffraction pattern with characteristic d-values (in A°) percentage (in %) as shown in the following table.

d-values	Intensity (%)
10.2972	35
8.5646	6
7.6618	22
7.4935	21
7.3691	21
6.6317	25
6.5246	29
6.2320	87
5.7713	7
5.7121	9
5.3042	20
5.2174	6
4.9733	34
4.8335	7
4.7614	5
4.7162	8
4.6284	27
4.4802	13
4.3795	54
4.3163	77
4.2874	100
4.2308	21
4.1297	34
4.0958	34
4.0117	17
3.8275	24
3.7263	13
3.6509	17
3.5311	6
3.3141	29
3.2782	18
3.1207	17
3.0035	5

d-values	Intensity (%)
2.8824	5
2.8099	8
2.8014	6
2.0562	6

3. The crystalline polymorph Form-VI of Olanzapine of claim 2, having an X-ray powder diffraction pattern as depicted in Figure (1).

4. The crystalline polymorph Form-VI of Olanzapine of claim 1, having differential scanning calorimetry thermogram which exhibits a characteristic endo peak around 196°C.

5. The crystalline polymorph Form-1 of Olanzapine of claim 4, having a differential scanning calorimetry thermogram as depicted in Figure (2).

6. The crystalline polymorph Form-VI of Olanzapine of claim 1, having identified characteristic peaks around 3217 cm^{-1}, 2933 cm^{-1}, 1592 cm^{-1}, 1561 cm^{-1}, 1468 cm^{-1}, 1369 cm^{-1}, 1218 cm-1, 1143 cm^{-1}, 1007 cm^{-1}, 964 cm^{-1}, 751 cm^{-1} and 674 cm^{-1} in the Infra red Spectrum.

7. The crystalline polymorph Form-VI of Olanzapine of claim 6, having an Infrared spectrum as depicted in Figure (3).

8. A process for the preparation of novel crystalline polymorph Form-VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2, 3-b] [1,5]benzodiazepine (Olanzapine), which comprises;

(i) stirring polymorph Form-I of Olanzapine in a C_1-C_6 alkanol at a temperature of 0 to 40°C for 30 minutes to 10 hours;

(ii) isolating the obtained solid form step (i) by conventional methods; and

(iii) drying the compound of step (ii) at a temperature of 40 to 100°C to afford the desired crystalline polymorph Form-VI of Olanzapine.

9. The process as claimed in claim 8, of step (i), wherein the said alcohol is n-butanol or tert-butanol.

10. A composition comprising novel crystalline Form VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b] [1,5] benzodiazepine according to any one of claims 1 to 7 and pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, binder, stabilizer, solvent or solvate.

11. The composition according to claim 10, in the form of a tablet, capsule, lozenge, powder, syrup, solution, suspension, ointment, or dragee.

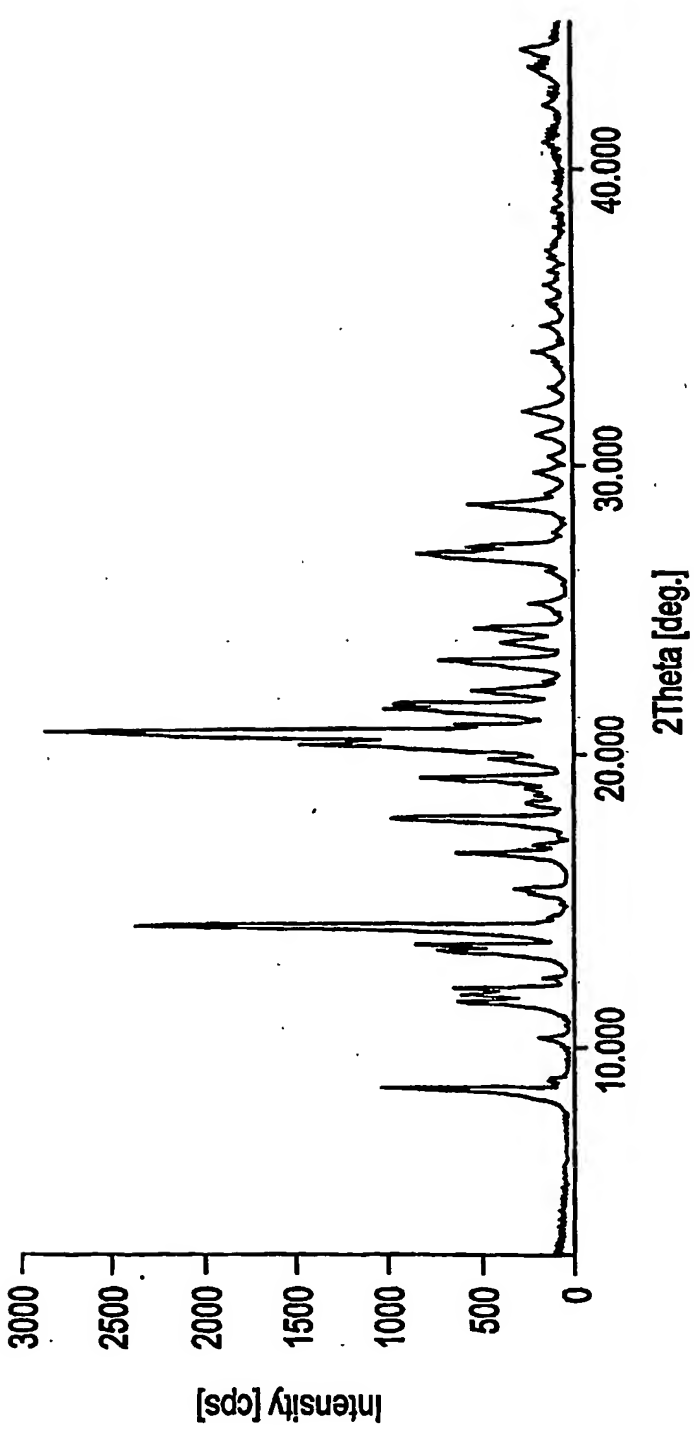
12. The composition according to any one of claims 10 or 11, for the treatment of a disorder of the central nervous system.

13. A method for treating a disorder of the central nervous system comprising administering an effective amount of crystalline Form VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b] [1,5] benzodiazepine according to any one of claims 1-7 and a pharmaceutically acceptable carrier, diluent, excipient, additive, filler, lubricant, binder, stabilizer, solvent or solvate to a patient in need thereof.

14. A medicine for the treatment of a disorder of the central nervous system comprising an effective amount of crystalline Form VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b] [1,5] benzodiazepine according to any one of claims 1-7.

15. Use of crystalline Form VI of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b] [1,5] benzodiazepine according to any one of claims 1-7 for the preparation of a medicament for the treatment of a disorder of the central nervous system.

FIG. 1


Intensity [cps]
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2500
2000
1500
1000
500
0
10.000
20.000
30.000
40.000
2Theta [deg.]

FIG. 2

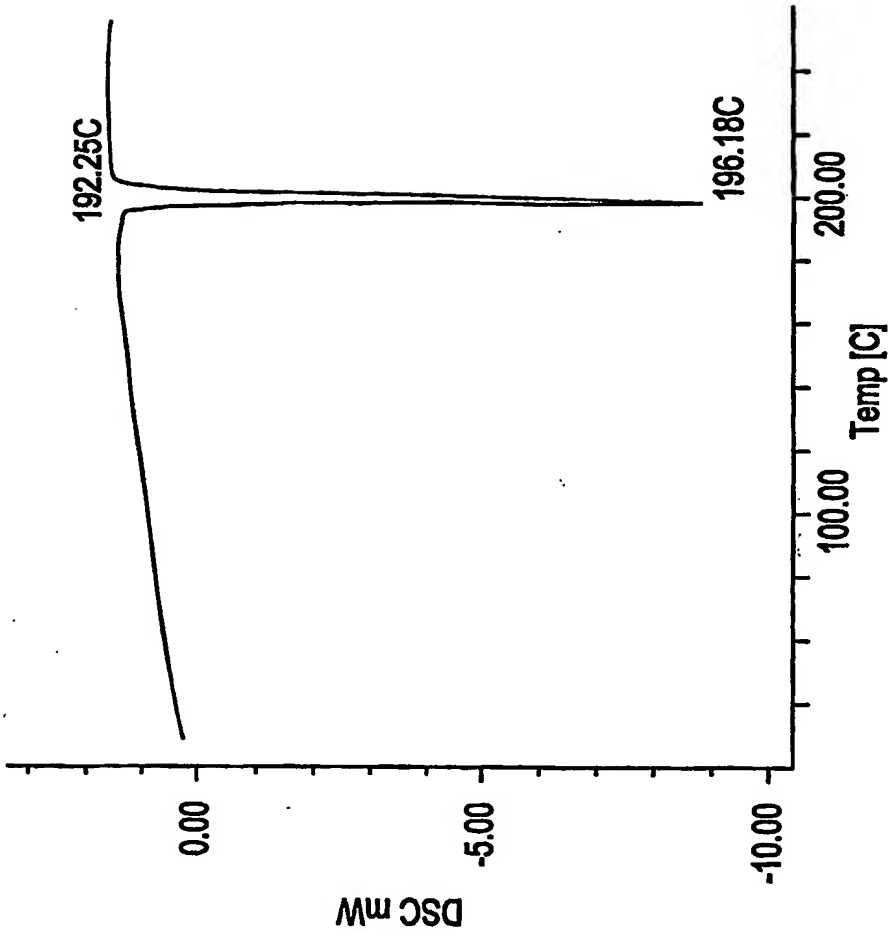
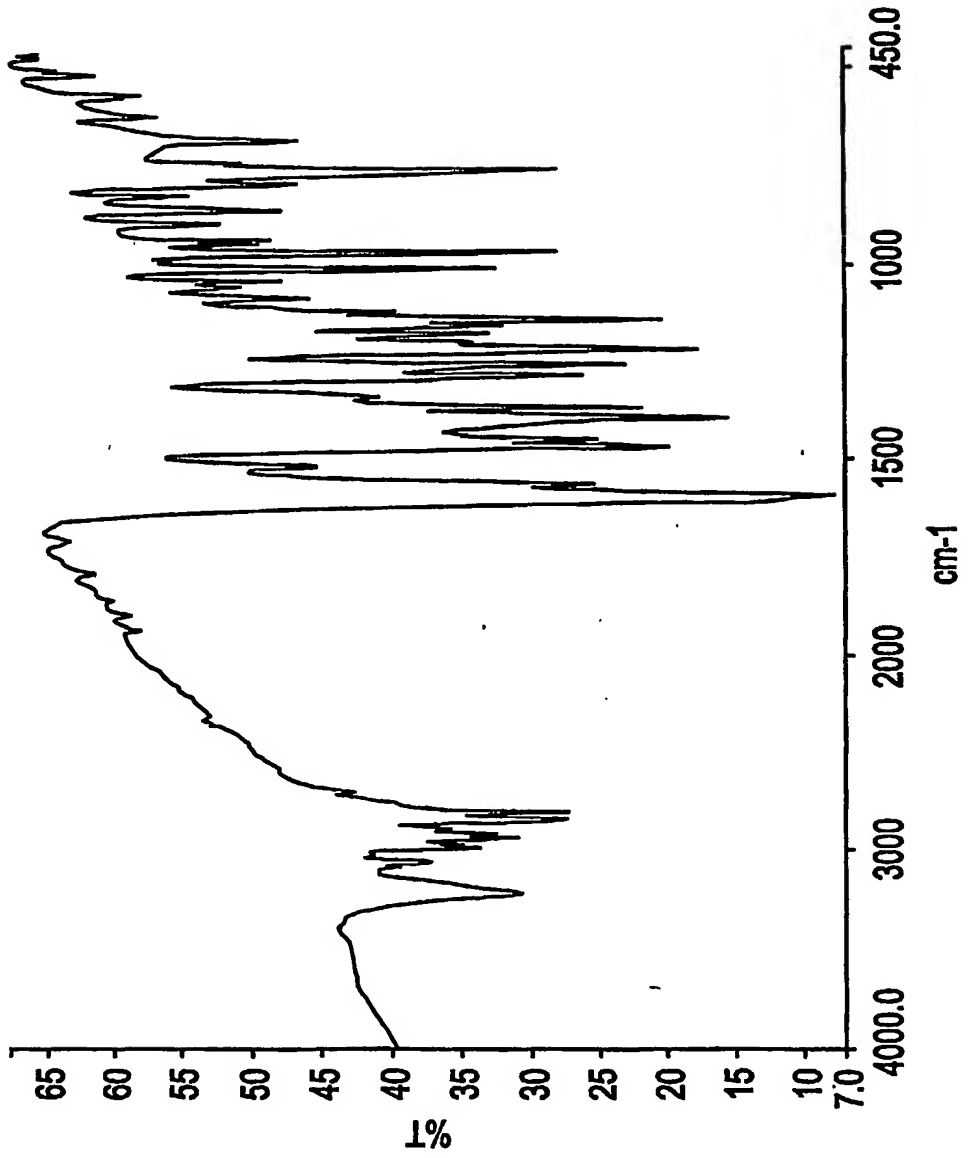


FIG. 3


450.0
1000
1500
2000
3000
4000.0
cm-1
65
60
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/12414

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 A61K31/55 A61P25/00 //(C07D495/04,333:00, 243:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 348 458 B1 (KANKAN RAJENDRA N ET AL) 19 February 2002 (2002-02-19) cited in the application claims 9-11 ---	1-15
Y	EP 0 831 098 A (LILLY CO ELI) 25 March 1998 (1998-03-25) cited in the application claim 9 ---	1-15
Y	WO 02 18390 A (CHAKKA RAMESH ;REDDY S LAB LTD DR (IN); REGURI BUCHI REDDY (IN); K) 7 March 2002 (2002-03-07) examples 3-6 --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 July 2003	04/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bakboord, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y,P	WO 02 060906 A (GANO JAMES EDWARD ;DAVIES JULIAN (US); GENEVA PHARMACEUTICALS INC) 8 August 2002 (2002-08-08) claims 1-13	1-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/12414

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